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OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

TXR No. 0054170

MEMORANDUM

DATE: March 28, 2006

SUBJECT: **Metofluthrin:** Qualitative Risk Assessment Based On Wistar (HanBrl: WIST {SPF}) Rat Carcinogenicity Dietary Study

P.C. Code: 109709

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BACKGROUND

A combined chronic toxicity/carcinogenicity study in Wistar (HanBrl: WIST [SPF]) rats was conducted by RCC Ltd., Toxicology, Itingen, Switzerland, for Sumitomo Chemical Company, Osaka, Japan, and dated July 7, 2005 (Laboratory Study No. 846244, MRID No. 46611301).

The study design allocated groups of 50 rats per sex to dose levels of 0, 20, 200, 900 or 1800 ppm (0, 0.8, 8.2, 38.1 or 77.8 mg/kg/day for males; 0, 1.0, 10.1, 47.4 or 96.1 mg/kg/day for females) of Metofluthrin for 104 weeks. An additional 20 rats per sex per dose were designated for interim sacrifice at week 53.

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ANALYSES

Survival Analyses

There were no statistically significant incremental changes in mortality with increasing doses of Metofluthrin in male rats (Table 1). Female rats showed a statistically significant decreasing trend for mortality at $p < 0.05$ (Table 3).

Tumor Analyses

Male rats had a statistically significant trend, and statistically significant pair-wise comparisons of the 1800 ppm dose group with the controls, for liver carcinomas and adenomas and/or carcinomas combined, all at $p < 0.01$. There was a statistically significant trend for liver adenomas at $p < 0.05$. There was also a statistically significant pair-wise comparison of the 900 ppm dose group with the controls for liver adenomas and/or carcinomas combined at $p < 0.05$. The statistical analyses of the male rats were based upon the Exact test for trend and Fisher's Exact test for pair-wise comparisons (Table 2).

Female rats had statistically significant trends at $p < 0.01$, and statistically significant pair-wise comparisons of the 1800 ppm dose group with the controls at $p < 0.05$, for liver adenomas and liver carcinomas. There was also a statistically significant trend at $p < 0.01$, and statistically significant pair-wise comparisons of the 900 ppm dose group with the controls at $p < 0.05$ and of the 1800 ppm dose group with the controls at $p < 0.01$, for liver adenomas and/or carcinomas combined. The statistical analyses of the female rats were based upon Peto's Prevalence test due to a statistically significant decreasing trend for mortality with increasing doses of Metofluthrin (Table 4).

Table 1. Metofluthrin – Wistar (HanBrl: WIST [SPF]) Rat Study (MRID 46611301)

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Weeks

Dose (ppm)	1-26	27-52	53[i]	53-78	79-106[f]	Total
0	0/70	7/70	20/63	1/43	12/42	20/50 (40)
20	1/70	8/69	18/61	5/43	9/38	23/52 (44)
200	0/70	9/70	20/61	4/41	11/37	24/50 (48)
900	0/70	11/70	20/59	3/39	5/36	19/50 (38)
1800	1/70	9/69	19/60	1/41	8/40	19/51 (37)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.
[f]Final sacrifice at weeks 104-106.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Metofluthrin – Wistar (HanBrl: WIST [SPF]) Rat Study (MRID 46611301)

Male Liver Tumor Rates[+] and Fisher's Exact Test and Exact Test for Trend Results

	Dose (ppm)				
	0	20	200	900	1800
Adenomas (%)	1/68 (1)	1/68 (1)	3[a]/69 (4)	5/70 (7)	6[a]/69 (9)
p =	0.01091*	0.75185	0.31525	0.11105	0.06002
Carcinomas (%)	0/68 (0)	0/68 (0)	0/69 (0)	3[b]/70 (4)	8[b]/69 (12)
p =	0.00001**	1.00000	1.00000	0.12774	0.00335**
Combined (%)	1/68 (1)	1/68 (1)	3/69 (4)	8/70 (11)	12[c]/69 (17)
p =	0.00001**	0.75185	0.31525	0.01845*	0.00119**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.

[a]First adenoma observed at week 52, simultaneously at 200 and 1800 ppm.
[b]First carcinoma observed at week 52, simultaneously at 900 and 1800 ppm.
[c]Two animals in the 1800 ppm dose group had both an adenoma and a carcinoma.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Metofluthrin – Wistar (HanBrl: WIST [SPF]) Rat Study (MRID 46611301)

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Weeks

Dose (ppm)	1-26	27-52	53[i]	53-78	79-106[f]	Total
0	6/70	0/64	15/64	1/49	10/48	17/55 (31)*[n]
20	5/70	0/65	15/65	2/50	16/48	23/55 (42)
200	15/70	1/55	5/54	3/49	7/46	26/65 (40)
900	11/70	1/59	10/58	0/48	10/48	22/60 (37)
1800	5/70	1/65	14/64	0/50	6/50	12/56 (21)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.
[f]Final sacrifice at weeks 104-106.
[n]Negative trend.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Metofluthrin – Wistar (HanBrl: WIST [SPF]) Rat Study (MRID 46611301)

Female Liver Tumor Rates+ and Peto's Prevalence Test Results

	Dose (ppm)				
	0	20	200	900	1800
Adenomas (%)	1/38 (3)	1/32 (3)	0/40 (0)	3/38 (8)	7[a]/46 (15)
p =	0.00184**	0.45123	0.84449	0.15372	0.03857*
Carcinomas (%)	0/40 (0)	2/37 (5)	1[b]/42 (2)	2/40 (5)	7/47 (15)
p =	0.00241**	0.10896	0.15866	0.07726	0.01653*
Combined (%)	1/40 (3)	3/37 (8)	1/42 (2)	5/40 (13)	12[c]/47 (26)
p =	0.00007**	0.17116	0.50366	0.04548*	0.00407**

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

[a]First adenoma observed at week 104, dose 1800 ppm.
[b]First carcinoma observed at week 100, dose 200 ppm.
[c]Two animals in the 1800 ppm dose group had both an adenoma and a carcinoma.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose-level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

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